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Original article

Comparison between blood ketone and blood gas analysis indices in management of diabetic ketoacidosis

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Abstract

Objective: Blood ketone monitoring is commonly used in the management of diabetic ketoacidosis (DKA). However, bedside ketone meters have limited availability in hospitals. This study aimed to clarify the correlation between blood ketones and blood gas analysis (BGA) in the treatment of DKA and thereby identify parameters that can be used as surrogates for blood ketones.

Patients and Methods: This retrospective observational study included patients with DKA admitted to the JA Toride General Medical Center between November 2021 and March 2024. Multiple regression analysis was performed using blood ketone levels as the objective variable and BGA indices as explanatory variables. Additionally, the study evaluated 1) the time course of ketone levels and BGA indices during the DKA treatment and 2) the correlation between ketone levels and the BGA indices.

Results: Sixteen patients were enrolled. Multiple regression analysis showed that the corrected anion gap (cAG), defined as the anion gap minus lactate concentration, was a significant predictor of blood ketones. Among pH, HCO_3^-, and cAG, only cAG had significant regression coefficients (−0.061 [95% confidence interval (CI): −3.49 to 1.98], −0.233 [−0.156 to 0.0118], 0.636 [0.129 to 0.246], respectively; coefficient of determination: 0.765). The correlation coefficient between cAG and blood ketone levels was high (0.9694).

Conclusion: cAG levels strongly correlate with blood ketone concentrations and may serve as a surrogate marker for blood ketones in the management of DKA. Because measurements of the anion gap and lactate concentrations are inexpensive and widely available in most medical facilities, cAG is a promising indicator for DKA management.

Key words: diabetic ketoacidosis, management, blood ketone, blood gas analysis, corrected anion gap

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Introduction

Diabetic ketoacidosis (DKA) is a severe and common complication of diabetes mellitus (DM)[1]. Recently, the measurement of blood ketones in preference to urine ketones has become an established tool for the management of DKA[2]. A systematic review demonstrated the benefits of point-of-care testing (POCT) for blood ketone measurement, showing reduction in the time required for DKA recovery and the duration of hospital admission[3]. Furthermore, a study conducted in the intensive care unit (ICU) reported that monitoring blood ketone levels in patients with DKA led to shorter ICU stays and overall healthcare cost savings of nearly 3,000 euros compared to monitoring patients with urine ketones[4]. In line with these findings, the international society for pediatric and adolescent diabetes (ISPAD) and U.K. Joint British Diabetes Societies (JBDS) guidelines recommend monitoring blood ketones during treatment of DKA[5, 6]. The ISPAD guidelines suggest measuring β-hydroxybutyrate (the major ketone in DKA) every 2 h at approximately 0.5 mmol/L/h until concentrations fall below 1 mmol/L. Simi-

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larly, the JBDS guidelines recommend repeated measurement of β-hydroxybutyrate, to achieve a reduction of at least 0.5 mmol/L/h.

In contrast, the American Diabetes Association (ADA) guidelines recommend continuous intravenous insulin administration until "ketonemia is controlled" but do not specify how to assess this[7]. This discrepancy among guidelines may be partly attributed to varying availability of POCT for blood ketones across countries. For example, a 2014 UK survey showed that 76% of institutions had access to POCT for blood ketones[8]. In contrast, the availability of quality-controlled POCT for blood ketones in the U.S. remains unclear, as the Food and Drug Administration does not require the same quality checks for POCTs of blood ketones as for laboratory tests[2].

In Japan, the number of medical institutions equipped with POCT for blood ketones is limited. Therefore, this study explored the feasibility of substituting blood ketone in conventional blood gas analysis (BGA). Specifically, we compared blood ketone levels and BGA indices obtained simultaneously during DKA treatment.

Patients and Methods

Study population

Patients admitted to the JA Toride General Medical Center for DKA between November 2021 and March 2024 were included if their blood ketone levels were measured multiple times. DKA was diagnosed according to JBDS guidelines[6]. Briefly, the diagnostic criteria included blood glucose >200 mg/dL (>11 mmol/L), pH <7.3 and/or HCO_3^- <15 mmol/L, and blood ketone >3 mmol/L. Blood ketones were measured with StatStrip® (Nova Biomedical, Waltham, MA, USA). BGA was performed using the ABL90 FLEX® (Radiometer, Copenhagen, Denmark).

Study design

This single-center, retrospective, observational study compared changes in blood ketone, pH, HCO_3^-, anion gap (AG), and lactate levels over time after DKA treatment. Multiple regression analysis was performed with blood ketones as the objective variable and BGA indices as explanatory variables in the treatment of DKA. Changes in blood ketone levels and BGA indices over time during DKA treatment were also compared. Furthermore, correlations between blood ketones and key parameters including pH, HCO_3^-, AG, and corrected anion gap (cAG, defined as the anion gap minus lactate concentration) were analyzed.

Statistical analysis

Results are expressed as means ± standard deviation (SD). The results of the multiple regression analysis were expressed as the coefficient of determination and standardized regression coefficient with a 95% confidence interval (CI) for each explanatory variable. Pearson's correlation coefficient was used to evaluate the correlation between blood ketone levels and BGA indices. All statistical analyses were performed using the Statcel 4 software (OMS Publishing Inc., Saitama, Japan).

Study approval

This study was approved by the Human Ethics Review Committee of the JA Toride General Medical Center (approval no. 531) and was conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments.

Results

Patient characteristics

Sixteen patients diagnosed with DKA were included in this study. Their characteristics at the time of DKA diagnosis are presented in Table 1. The cohort comprised nine women, with a median age of 67 years (range: 26–90 years). Five patients had type 1 diabetes mellitus, and eleven had type 2 diabetes.

Regarding laboratory data, the mean levels of blood ketone, pH, HCO_3^-, AG, lactate were 5.68 ± 1.45 mmol/L, pH 7.13 ± 0.19, 9.64 ± 5.04 mmol/L, 30.8 ± 5.51 mmol/L, 3.17 ± 1.33 mmol/L, respectively.

Associations between blood ketones and pH, HCO_3^-, and cAG

The results of the multiple regression analysis are summarized in Table 2, with a coefficient of determination of 0.765. Among the variables analyzed (pH, HCO_3^-, and cAG), only cAG showed a significant correlation with blood ketone levels (standard regression coefficient of 0.636 [0.129–0.246]). The regression coefficient for pH; was −0.061 [95%CI: −3.49 to 1.98] and HCO_3^- was −0.233 [−0.156 to 0.0118]).

Changes over time in blood ketones, pH, HCO_3^-, AG, cAG, and lactate during the treatment of DKA

Figure 1 shows the changes in blood ketone, pH, HCO_3^-, AG, cAG, and lactate levels over time during DKA treatment. Blood ketone and cAG levels decreased linearly during the first few hours of treatment. Lactate levels also tended to decrease after treatment initiation but were highly variable. HCO_3^- and pH increased at the start of treatment, with particularly large fluctuations observed in HCO_3^- .

Correlations between blood ketones and pH, HCO_3^-, AG, cAG

Figure 2 shows the correlations between blood ketone

Table 1 Patient characteristics at the diagnosis of diabetic ketoacidosis (DKA)

	Patients registered (N=16), mean ± SD
Female, n (%)	9 (56)
Age (years)	
Median	67
Range	26–90
Diabetes type, n (%)	
Type 1	5 (31)
Type 2	11 (69)
Disease duration (years)	
Median	4
Range	0–33
GCS	
Median	15
Range	8–15
HR (/min)	114.2 ± 21.4
sBP (mmHg)	126.4 ± 26.3
dBP (mmHg)	74.3 ± 12.8
RR (/min)	25.3 ± 5.0
Blood glucose (mg/dL)	556.8 ± 239.1
HbA1c (%)	11.0 ± 3.5
BUN (mg/dL)	38.8 ± 13.4
Cre (mg/dL)	1.14 ± 0.41
Na (mEq/L)	134.4 ± 9.7
K (mEq/L)	5.06 ± 0.95
Cl (mEq/L)	97.0 ± 10.0
iP (mg/dL)	6.0 ± 1.4
pH	7.13 ± 0.19
pCO2 (mmHg)	25.5 ± 11.8
HCO3 (mmol/L)	9.64 ± 5.04
Anion gap (mmol/L)	30.8 ± 5.51
Blood ketone (mmol/L)	5.68 ± 1.45
Lactate (mmol/L)	3.17 ± 1.33

AG: anion gap; BUN: blood urea nitrogen; Cl: chloride; Cre: creatinine; dBP: diastolic blood pressure; GCS: Glasgow Coma Scale; HbA1c: hemoglobin A1c; HCO_3: bicarbonate; HR: heart rate; iP: inorganic phosphate; K: potassium; Na: sodium; RR: respiration rate; sBP: systolic blood pressure; pCO_2: partial pressure of carbon dioxide.

Table 2 Associations between blood ketones and pH, HCO_3^-, and cAG in the treatment of diabetic ketoacidosis (DKA)

	Standard regression coefficient	95% confidence interval	
		Lower limit	Upper limit
pH	−0.061	−3.49	1.98
HCO_3	−0.233	−0.156	0.0118
cAG	0.636	0.129	0.246
Coefficient of determination=0.765			

cAG: corrected anion gap defined as the anion gap minus lactate; HCO_3: bicarbonate.

levels and pH, HCO_3^-, AG, and cAG. The correlation coefficients were as follows: pH, 0.9003; HCO_3^-, 0.9606; AG, 0.9492; and cAG, 0.9694.

Discussion

This study demonstrated that among pH, HCO_3^-, and cAG, only cAG could predict blood ketones (Table 2). Previous reports have not shown significant correlations between blood ketones and traditional factors associated with DKA treatment, such as pH, HCO_3^-, AG, and blood glucose levels[9, 10]. Lactate concentrations are often elevated in DKA[11], and AG is often high in the presence of hyperlactatemia[12]. Therefore, hyperlactatemia may cause a discrepancy between blood ketones and AG, necessitating correction for lactate to predict blood ketones from AG. In fact, a strong correlation was observed between cAG and blood ketone levels throughout DKA treatment (Figure 2).

End-stage kidney disease (ESKD) may also influence the relationship between AG and blood ketone levels. One study showed that, compared to individuals with normal renal function, patients with DKA and ESKD had higher AG (23.7 ± 7.6 vs. 19.5 ± 4.7 mmol/L, $P<0.01$) and lower blood β-hydroxybutyrate levels (4.3 ± 3.3 vs. 5.9 ± 2.5 mmol/L, $P=0.01$)[13]. Because this study did not include patients with ESKD patients, it is unknown whether the rate of decline in cAG during DKA treatment correlates with the rate of decline in β-hydroxybutyrate in this population. Therefore, further research is required in this area.

The most critical question for clinicians during the initial hours of DKA treatment is, "Is the current treatment working?". To assess this, both the magnitude of the indicator and its change after treatment are important. Blood ketone and cAG levels showed a linear decrease in the first 8–10 h after starting DKA treatment (Figure 1). In contrast, pH and HCO_3^- increased after the initiation of DKA treatment; however, this trend was not monotonic. Furthermore, large deviations, especially for HCO_3^-, indicated that it was not a useful measure for assessing treatment success a few hours after treatment initiation.

DKA-associated complications such as hypoglycemia and hypokalemia, can be avoided with low-dose insulin therapy[11]. Given that the amount of insulin required to inhibit lipolysis and ketone production is less than that required to inhibit hepatic gluconeogenesis and enhance peripheral glucose uptake[14], the insulin dose of insulin administration may be lower when blood ketones are used as markers for DKA treatment. In this study, intravenous insulin was adjusted and administered until a decrease in blood ketone levels was observed. In 11 of 16 patients, intravenous insulin was changed to subcutaneous administration within 24 h. A rapid reduction in insulin dose can i) reduce the frequency of complications associated with insulin therapy,

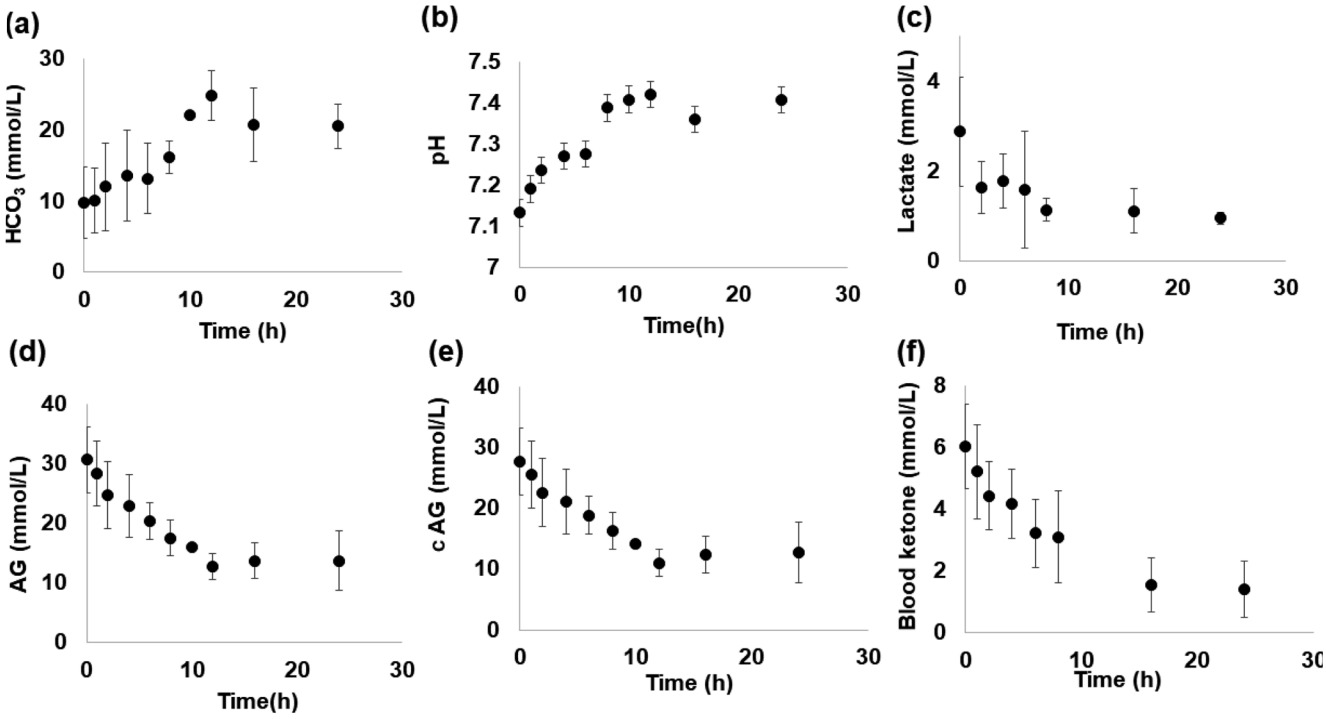

Figure 1 Changes over time in blood ketones, pH, HCO_3^-, AG, cAG, and lactate during the treatment of DKA
AG, anion gap; cAG, corrected anion gap defined as the anion gap minus lactate; HCO_3, bicarbonate.

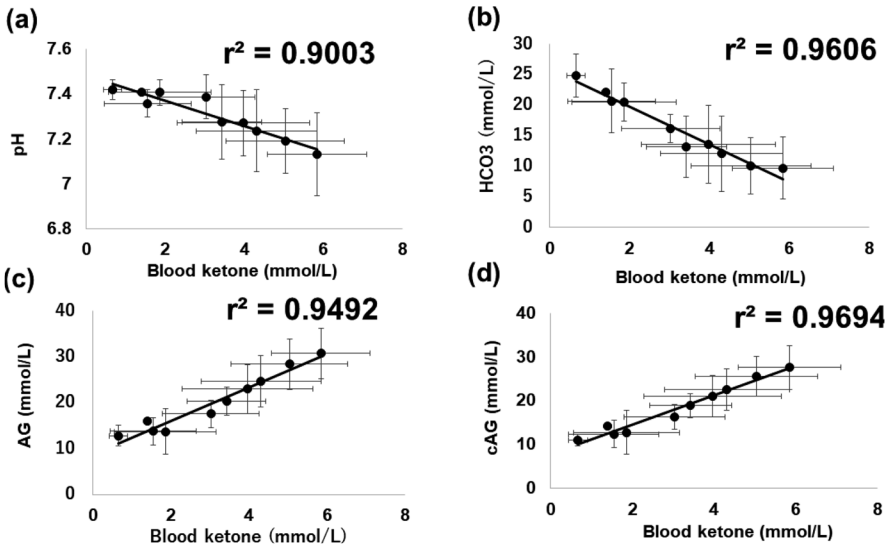

Figure 2 The correlation between blood ketones and pH, HCO_3^-, AG, and cAG
AG, anion gap; cAG, corrected anion gap defined as the anion gap minus lactate; HCO_3, bicarbonate; r^2, correlation coefficient.

such as hypoglycemia and hypokalemia, and ii) shorten the duration of DKA treatment, which can lead to shorter hospital stays. Therefore, DKA can be treated using blood ketones and cAG as treatment indicators.

Several remission criteria have been proposed for DKA. For example, the ADA criteria for DKA resolution include serum glucose level <200 mg/dL and two of the following: serum bicarbonate level ≥15 mEq/L, pH >7.3, and anion gap ≤12 mEq/L[7]. Once the remission criteria are reached, it is suggested that insulin administration be switched to subcutaneous injections and that the patient resumes oral intake. The relationship between these remission criteria and blood

ketones is unclear, especially because blood glucose has no direct relationship with blood ketones[14]. The relationship between blood ketone levels and DKA remission warrants further investigation.

Over the last decade, many reports have been published on euglycemic diabetic ketoacidosis without hyperglycemia related to SGLT-2 inhibitors[15–17]. JBDS recommends initiating continuous intravenous insulin infusion at 0.1 unit/kg/h while infusing 10% dextrose at a rate of 125 mL/h in euglycemic ketoacidosis[18]. In such cases, blood glucose levels are not indicative of successful DKA treatment. Further investigation is needed to determine which treatment method would be beneficial for euglycaemic ketoacidosis in facilities where POCT for blood ketone measurements is not available. The results of this study suggest that cAG can be used to monitor the initial treatment of euglycaemic ketoacidosis.

In conclusion, blood ketones are useful indicators for DKA treatment, and cAG can be used as a surrogate marker for blood ketones. In Japan, POCT for blood ketones can be performed at some medical institutions but is not fully utilized. The advantage of the POCT of blood ketones is its quantitative nature, allowing its use as an indicator of treatment progress. Since POCT for blood ketones is not widely available in the U.S., the ADA guidelines do not describe specific procedures for managing DKA with POCT for blood ketones. However, the medical environments in the U.S. and Japan differ. It is desirable to build evidence of the Japanese medical situation and develop guidelines for the management of DKA that are compatible with the actual situation in Japan.

Conclusions

This study demonstrated a strong correlation between blood ketone and cAG levels during DKA treatment. These findings suggest that cAG may be a useful surrogate marker of blood ketones. AG and lactate concentrations can be measured in most hospitals and the cost of measurement is low. Therefore, it would be beneficial to use cAG as a surrogate marker for blood ketone levels.

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Author contribution: HY conceived the idea and drafted the original manuscript. AH, TS, AO, and TI were responsible for data acquisition and analysis. All the authors discussed the data and commented on the manuscript. All authors approved the final manuscript before submission.

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